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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,428	07/07/2003	Stephen S. Navran JR.	SYNT-P001US	8590

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EXAMINER	
WAX, ROBERT A	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,428	NAVRAN ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The current application filed on July 7, 2003 claims priority to provisional application, 60/394,597 filed on July 9, 2002 and to provisional application 60/430,795 filed on December 4, 2002.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 the word "comprising" is missing between "molecule" and the colon that follows it, the word "identify" should be "identifying" for consistency, in parts (d), (e) and (f) the word "media" should be "medium". This point also applies to claims 16, 18 (e) and (f) and 23 (f), (g), (h), (i) and (j). Additionally, step (f), the isolation step, will only work if the proteinaceous molecule is secreted from the cell. If it isn't secreted, there will be no protein to isolate since the cells are not lysed.

Claim 7 is incorrect in two respects. First, it should depend from claim 6 rather than claim 1. Second, bioselection by antibiotic resistance would not work in a mammalian cell since antibiotics already have no effect on mammalian cells. This point also applies to claim 21.

The term "excrete" appears in claims 18 (f) and 23 (h) and (i). It seems that the word "secrete" would be more appropriate.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 2, 6, 9, 10, 14, 15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650).

Rai et al. teach generally how to select an expression system to make a desired recombinant protein. At page 1124, under the heading Mammalian cells the first sentence says, "Ideally, proteins requiring mammalian post-translational modifications should be expressed in mammalian cells." They go on to say that where "product authenticity is absolutely essential for clinical efficacy, then . . . a mammalian host is the only choice."

Verma et al. compare different expression systems for antibodies, discussing mammalian cells in Section 7, pages 174-176. They point out the value of mammalian cell expression as "the signals for synthesis, processing and secretion of eukaryotic proteins are properly and efficiently recognized." On page 175 they discuss commonly used selectable markers. Although the specific proteins in Verma et al. are antibodies, their teachings of what is conventional when using mammalian expression systems are extendable to other proteins.

The combined teachings of Rai et al. and Verma et al. show that those of ordinary skill in the art know when to choose to express the recombinant protein in mammalian cells and how to do it. They teach that it is conventional, even preferred, to express proteins in cells as close to the originals as possible, especially when the protein is intended for pharmaceutical use. Then the glycosylation and secretion are

critical for the end use. Further, they teach that it is conventional to use a selectable marker along with the gene of interest so the successfully transfected cells can be located within the colonies of cells. The difference between these teachings and the instant claims is the use of the rotating reactor.

Spaulding et al. teach expression of recombinant proteins in insect cells within a horizontally rotating culture vessel modulated to create low shear conditions. The background of the invention section discusses production of recombinant proteins from animal cells ant the difficulties involved therein. At column 3, lines 29-55 they teach why low hydrodynamic forces are essential for animal cells. Their discussion continues with regard to insect cells but they make it clear that their so-called HARV would be ideal for cultivation of animal cells making recombinant proteins as well as insect cells. At column 13, line 14 – column 15, line 9 they compare results obtained with HARV to results obtained in a shaker flask and show that cells grown in HARV lived longer and made more protein than cells cultured in shaker flasks. Spaulding et al. do not specifically show the exact steps in claim 1 but do show similar steps for insect cells.

Schwarz et al. teach a rotating bioreactor suitable for practicing the instant invention, as admitted in the instant specification.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to select mammalian expression systems when expressing mammalian proteins in accordance with the combined teachings of Rai et al. and Verma et al. It would further have been obvious to one of ordinary skill in the art at the time the invention was made to use a rotating bioreactor that produces both a low shear and low

gravity environment to express recombinant proteins from mammalian cells in view of the teachings of Spaulding et al. who did the same thing for insect cells. They point out that insect cells are even more fragile than mammalian cells and lead one to the conclusion that culturing mammalian cells in a similar environment to the one they like for insect cells would be expected to achieve both longer-lived cells and more yield of the desired protein.

7. Claims 1 - 6, 9, 10, 14, 15 and 18 - 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) as applied to claims 1, 2, 6, 9, 10, 14, 15 and 18 above, and further in view of Morrow et al. and Julkunen et al.

This rejection focuses on the additional limitations recited in claims 3-5, 19 and 20. Both Morrow et al. and Julkunen et al. teach information about human placental protein 14 (PP14), its importance and how to make it recombinantly.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express PP14 in the rotating cell culture apparatus of Schwarz et al. (as discussed above in combination with the teachings of Rai et al., Verma et al. and Spaulding et al.) in view of the teachings of Morrow et al. and Julkunen et al. Morrow et al. teach that PP14 may have utility to inhibit lymphocyte proliferation; this provides motivation to express large quantities of the protein. They use K562 cells as the host cells; one of ordinary skill in the art would have found it obvious to do the same in order to achieve the same beneficial results.

8. Claims 1, 2, 6, 9, 10 – 15, 18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) as applied to claims 1, 2, 6, 9, 10, 14, 15 and 18 above, and further in view of Anderson et al.

This rejection focuses on the additional limitations recited in claims 11-13 and 22-25. Anderson et al. teach an improvement in the rotating cell culture device of Schwarz et al. incorporating filters transversing the space within the bioreactor to subdivide the space while still permitting enhanced flow of medium containing nutrients and oxygen. Anderson et al. do not teach their filters specifically having a cutoff of a particular molecular weight.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to culture mammalian cells in the bioreactor of Anderson et al. rather in the bioreactor of Schwarz et al. in order to obtain the benefits taught by Anderson et al. It is considered to be within the ordinary level of skill in the art to select the pore size of the filters to either trap the secreted protein or let it through to be remove by the flowing medium, presumably, to be trapped further downstream by a filter with the appropriate pore size to capture the molecule.

9. Claims 1, 2, 6, 9, 10, 14, 15, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) as applied to claims 1, 2, 6, 9, 10, 14, 15 and 18 above, and further in view of Hirao et al. and Morris et al.

This rejection focuses on the additional limitations recited in claim 16. Hirao et al. and Morris et al. each teach the removal of serum albumin from recombinantly produced protein. See column 4, line 18-column 5, line 48 of Hirao et al. and column 17, lines 37-48 of Morris et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove the albumin from the recombinantly produced protein made according to the teachings of Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) since Hirao et al. and Morris et al. teach that it is conventional to do so.

10. Claims 1, 2, 6, 9, 10, 14, 15, 18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650), and further in view of Anderson et al. as applied to claims 1, 2, 6, 9, 10, 14, 15 and 18 above, and further in view of Hirao et al. and Morris et al.

This rejection focuses on the additional limitations recited in claim 26. The teachings of Hirao et al. and Morris et al. have been outlined above. It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove the albumin from the recombinantly produced protein made according to the teachings of Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650), and further in view of Anderson et al. since Hirao et al. and Morris et al. teach that it is conventional to do so.

11. Claims 1, 2, 6, 8, 9, 10, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) as applied to claims 1, 2, 6, 9, 10, 14, 15 and 18 above, and further in view of Brucato et al.

This rejection focuses on the additional limitations recited in claims 8 and 17. Brucato et al. teach purification of recombinantly produced protein by attaching a histidine tail and using a metal chelate column to bind the protein of interest (see column 4, lines 51-63). It would have been obvious to one of ordinary skill in the art at the time the invention was made to attach a histidine tail to a recombinantly produced protein made according to the teachings of Rai et al. and Verma et al. in view of Spaulding et al. and Schwarz et al. (US Patent 5,026,650) to permit easy purification of the protein since Brucato et al. teach that it is conventional to do so.

12. Applicants should note that Examiner has carefully read the examples and has analyzed them with respect to their use as evidence of unobviousness to overcome the above rejections. One example of evidence of unobviousness is a showing of unexpectedly superior results. The examples compare production of PP14 in the rotating cell culture apparatus and a spinner flask and show that results obtained by the rotating apparatus are better. However, these results are expected from the teachings of Spaulding et al. who obtained the same superior results by using their so-called HARV. HARV and the instant rotating apparatus are similar enough to raise the expectation that similar improved results would be achieved by the rotating apparatus of

the instant case as were demonstrated by HARV. In responding to the above rejections, applicants are advised to take these comments into consideration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Wax
Primary Examiner
Art Unit 1653